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| EXAMINER | |
|---|---|
| BETTON, TIMOTHY E | |
| ART UNIT | PAPER NUMBER |
| 1617 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/617,078 | SCHWENDEMAN ET AL. | |
| | Examiner | Art Unit | |
| | TIMOTHY E. BETTON | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6 and 27-62* is/are pending in the application.

4a) Of the above claim(s) *27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 30-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicants' Remarks filed on 30 December 2008 have been filed and duly made of record.

The claim rejection under 35 U.S.C. § 103(a) is averred by applicants based on the alleged failure of Andrianov to teach the basic additive of magnesium carbonate. Further, applicants argue the properness of Sokoll in conjunction with Andrianov.

Applicants' arguments are fully considered but are not found persuasive. Applicants' art seems to suggest that the invention is principally drawn to magnesium carbonate as an active ingredient in view of the current invention. However, claim 1 clearly discloses biological effectiveness to the one or more antigens that may be incorporated and not to one or more basic additives.

Further magnesium carbonate is art-known as an excipient. Absent of any explanation and/or reasoning in the instant specification specifically directing the Examiner where it discloses that basic additives are the central thrust of the invention in terms of being primarily responsible for an immunological response is completely silent in the said specification.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the present invention is principally directed to the enhancing of an immunogenic response which is treated with antigens. Basic additives are just that- additives. The term excipients also fully encompass the additives based upon what agent is determined to be the active agent. Even in the alternate , additives serve the same purpose generally pharmaceutically

as far as helping to maintain stability thereby enhancing the potency and effectiveness of an active agent.

Applicants are seeming tot suggest that magnesium carbonate is the reason that the immunological response is enhanced when claimed invention is clearly directed to antigens/peptides as the central issue of the invention. In this case, as already made of record, Andrianov and Sokoll do adequately address peptides and antigens in obviousness of claimed invention.

Further, applicants' aver the teachings of Schoch and Lenntech over claim 4 but fail to offer evidence as to why these two references are not reasonably proper over claim 4. For the reasons already made of record, the teachings of Schoch and Lenntech are maintained.

Still further with regard to the Elahi, Wright, Thanavala in view Setterstrom in this current 103(a) rejection, applicants assertion that they do not teach each and every element in the invention has not been properly elucidated in the Remarks in such a way as to be persuasive in reasoning. Again, applicants' disclose these embodiments directed to the significance to magnesium carbonate enhancing immunogenic responses but the instant claim set does not reasonably suggest this so-called inventive objective.

For the reasons already made of record, the action of 30 September 2008 is maintained.

Absent of anything in the specification as suitable evidence to clearly aver the rejections of said claims, the current rejection is proper.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrianov et al. (USPN 5,529,777) in view of Sokoll et al (USPN 6,228,423 B1).

Andrianov et al. teach water soluble polymers or polymeric hydrogels [which] are used to encapsulate antigen to form vaccines. The antigen is mixed with a polymer solution, microparticles are formed of the polymer and antigen, and, optionally, the polymer is crosslinked to form a stable microparticle. Preferred polymers are alginate and polyphosphazenes, and mixtures thereof. Microparticles can be administered parenterally or mucosally. For oral delivery, the microparticles are preferably fifteen microns or less in diameter, and adhere to the mucosal lining of the gastrointestinal tract, increasing uptake by the reticuloendothelium. Andrianov et al. teach a polymeric/antigen delivery system (PLGA), that is biodegradable and biocompatible as also disclosed in subject claim1 (Column 4, lines 11-53).

Further, Andrianov et al. teach an antigen as a peptide in Column 12, line 29 of referenced patent as also disclosed in instant claims 2 and 3.Andrianov et al. teach the method wherein the antigen is selected from the group consisting of compounds derived from cells, bacteria, and virus particles, wherein the compound is selected from the group consisting of

proteins, peptides, polysaccharides, glycoproteins, glycolipids, and nucleic acids (column 26, lines 9-14). Thus, instant claim 2 is made obvious over Andrianov et al.

Additionally, Andrianov et al. teach a practicing method to elicit an immunogenic response incorporating said PLGA as is also disclosed in instant claim 1.

Furthermore, Andrianov et al. teach magnesium as a basic additive/multivalent cation incorporated with a polyelectrolyte preparation. Andrianov et al. does not teach the basic additive of magnesium carbonate. However, Examiner refers to Sokoll et al., which teach the immunogenic compositions comprising microparticles formed according to the present invention may be delivered in a manner to elicit an immune response at mucosal surfaces. Thus, the immunogenic composition may be administered to mucosal surfaces by nasal, oral (intragastric), buccal or rectal routes. Oral formulations may include normally employed excipients, such as pharmaceutical grades of saccharin, cellulose and magnesium carbonate.

Thus, it would be prima facie obvious to one of ordinary skill in the art to modify the invention of Andrianov et al. to accommodate the disclosure of magnesium carbonate in the formulation as in Sokoll et al. Both referenced. patents teach a PLGA directed to delivery of an antigen to a specific region in a mammal. Therefore, it would at once have been obvious to combine both references due to their relative similarity in scope of invention, i.e., delivery of antigen by a polymeric delivery system.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schoch, E.P. (Industrial and Engineering Chemistry; Direct Titrometric Methods for Magnesium, Calcium, and Sulfate Ions and Their Application in Water Analysis; 1926, Vol. 19, No.1, page 112) and CHEMTUTOR, LLC Acids and Bases; The 5% Rule, Copyright 1997, (page 17) in view of Lenntech (Magnesium (Mg) and water; Chemical Properties, Health and Environmental effects; Copyright 1998, page 1).

Schoch, E.P. teaches well-established pH value ranges for magnesium and magnesium ion at a pH of 10.23 as is encompassed in subject genus claim 4 of a pH of about 6.8 to about 12.5 for the basic additive of magnesium derivative/pharmacological salt.

Schoch does not teach the method of instant claim 1 wherein the basic additive is characterized by having a pH of a saturated solution at 37 degrees Celsius but instead of at 90-100 degrees Celsius (page1, 1st paragraph). CHEMTUTOR, LLC teach the measurement of pH in medicine, which is disclosed at 37 degrees Celsius, (page 17).

CHEMTUTOR, LLC does not teach magnesium carbonate, but does teach derivatives of magnesium and derivatives of carbonates. However, Examiner refers to Lenntech, which teaches water solubility of magnesium carbonate as being more soluble at (600mg/L) in

comparison to magnesium hydroxide at (12 mg/L)(page 1,4th paragraph). It further teaches that magnesium metals are not affected by water at room temperature and that magnesium generally is a slow- reacting element, but reactivity increases with oxygen levels (page 1, second paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the art disclosed in Schoch with that of CHEMOTUTOR, LLC. The teaching of properties and characteristics of magnesium carbonate in Lenntech would be the motivation to further combine the references of Schoch, CHEMOTUTOR, LLC and Lenntech. Claim 4 is directed to values, characteristics, and properties of magnesium carbonate already well-established in the pertinent art.

Claims 30-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elahi (USPN 4,280,816), Wright et al. (USPN 6,379,704 B2) and Thanavala et al. (Affinity, cross-reactivity and biological effectiveness of rabbit antibodies against a synthetic 37 amino acid C-terminal peptide of human chorionic gonadotropin, Clin exp. Immunol. (1980) 39, 112-118 in view of Setterstrom et al. (USPN 6,309,669 B1). ]

Elahi et al. teach a process for the immunoassay of antigens in a biological sample wherein an element comprised of particulate supported antibody loosely encapsulated and confined within a porous filter membrane material is utilized for addition to the biological sample. The method is particularly applicable to the radioimmunoassay (RIA) and enzyme-linked

immunoassay (ELIA) techniques for determining the presence and concentration of minute amounts of protein antigens in biological fluid samples, and for performing multiple assays utilizing these methods.

The process according to this invention may be practiced in a number of ways. Thus, for example, in one embodiment, antibody can be complexed (e.g., sorbed) onto the particulate solid support material, the particulates then loosely encapsulated in the rigid porous filter membrane, and the capsule element added to a biological sample containing labelled antigen. Alternatively, the particulate solid support material may have complexed thereon both the antibody and its labelled antigen prior to encapsulation and addition to a biological fluid.

For IgG, the conjugation between the enzyme, alkaline phosphatase and the IgG antigen is made by glutardialdehyde. 0.1 ml of a clear suspension of the enzyme solution is added to 0.1 ml of a solution containing 0.5 mg pure rabbit IgG. The mixture has a IgG-alkaline phosphatase ratio of 1:3 and dialyzed overnight against phosphate buffered saline. The contents are then reacted with 10 ul of 4.2% glutardialdehyde in phosphate buffered saline for 2 hours. The mixture is diluted to 1 ml with buffered saline, dialyzed overnight and separated on a Spharose 6B column in 0.05 M Tris-HCL buffer (pH 8.0). The eluted enzyme-labelled antigen is stabilized with 5% human serum albumin and stored at 4.degree. C. with 0.2% NaN.sub.3.

Wright et al. teach a method for preparing microparticles having a selected polymer molecular weight. The hold time and temperature of a solution containing a nucleophilic compound and a polymer having a starting molecular weight are controlled in order to control

the molecular weight of the polymer in the finished microparticle product. In this manner, a selected polymer molecular weight in the finished microparticle product can be achieved from a variety of starting material molecular weights (abstract only).

Wright et al teach administration of compound to a human subject (patient) (column 27, line 50).

Wright et al teach polymeric excipients (column 1, lines 48-67).

Wright et al. teach lactide: glycolide ratios with a disclosure of 100:0 (column 9, line 24)

Wright et al. teach PLGA 50:50 (column 12, line 52).

Wright does not teach human chorionic gonadotropin (hCG) or carboxyl terminal peptides.

However, Thanavala et al. does teach embodiments drawn to methods wherein the (hCG) antigen is a carboxyl terminal peptide of the beta subunit of (hCG) (Summary, page 112 and page 113, 2nd paragraph). Accordingly, Thanavala et al. teach antibodies with (hCG) were raised by immunizing rabbits with a synthetic peptide (see Summary. Page 112). Further, Thanavala specifically teach agglutination via a preparation of a (hCG) coated latex particles showed positive agglutination by day and were strongly positive by day 15 after immunization. Thus, it would be apparent to the skilled artisan that conjugation (i.e., covalent and/or ionic agglutination) is supported by the Thanavala et al. reference above.

Wright et al. and Thanavala et al. do not teach adjuvants.

However, Setterstrom et al teach adjuvants. Novel burst-free, sustained release biocompatible and biodegradable microcapsules, which can be programmed to release their active core for variable durations ranging from 1-100 days in an aqueous physiological

environment. The microcapsules are comprised of a core of polypeptide or other biologically active agent encapsulated in a matrix of poly (lactide/glycolide) copolymer, which may contain a pharmaceutically-acceptable adjuvant as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99 (abstract only).

Additionally, Setterstrom et al. teach administration to mammals (column 27, line 50).

Thus, it would have prima facie obvious to combine or incorporate together the teachings of Wright et al. with the teachings of Thanavala et al. Wright et al. teaches the objective and/or subject matter disclosed within instant claims which are directed to methods for preparing microparticles having a selected polymer molecular weight. Thanavala et al. provide the motivation to combine based on the disclosure directed to methods wherein the (hCG) antigen is a carboxyl terminal peptide of the beta subunit of (hCG). Wright et al. in turn discloses such microparticle formulations comprising examples of suitable biologically active agents including antigens. Setterstrom et al. further provides motivation by disclosing the general use of adjuvants in preparations of microparticles. Based on the explanation above, the skilled artisan would at once recognize the subject matter of Wright as being complementary with the limitations of Thanavala in regard to the mention of specific antigen types. Setterstrom et al. accordingly provides further evidence of the inclusion of variable and suitable biologically active agents, i.e., excipients and adjuvants.

Instant claims 30-62 are made obvious by the combined teachings of Wright et al, Thanavala et al. and Setterstrom et al.

Absent evidence to the contrary, the disclosed antigens encapsulated within the microparticles may also be interpreted based on the representation of the claims to be also conjugated to the microparticles.

Instant claims 42 –45 are drawn to characterization optimizations of magnitudes of ratio combinations of the basic additive in relation to the antigen of which it is coupled with in claimed invention. Similarly, the basic additive is compared in ratio strength to the biodegradeable polymer of which it is encapsulated. The skilled artisan would at once recognize the process of such optimizations of ratio magnitudes as a part of due and routine experimentation. Thus, instant claims 42-45 are made obvious due to the common practice in pharmacy technology to generate therapeutic ranges via extensive and routine experimentation.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB